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ALKYLSULFANYL-BENZENES AS FRAGRANCE COMPOUNDS

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This invention relates to alkylsulfanyl-benzenes, and in particular those having spicy and anisic odour notes, a method of producing the same and to flavour and fragrance compositions containing one or more of these compounds.

Compounds having spicy and anisic odour notes are of interest in the flavour and fragrance industry.

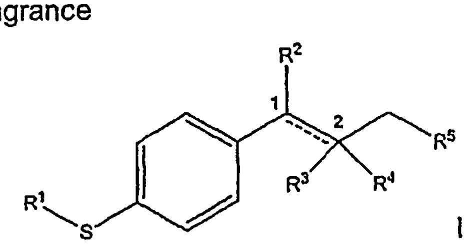
However, certain molecules, e.g. eugenol and anethole, despite having these interesting odour notes have the disadvantage that they discolour on storage, and therefore their use is usually limited to certain applications where discoloration is not a problem or can be masked.

Structural modification of these molecules, however, either results in a failure to retain the spicy and anisic odourant properties or the odourant properties are retained but they are far less intense and rich.

Accordingly, there remains a need to provide molecules that do not possess the disadvantages of the prior art molecules but which retain their spicy and anisic odour notes and are diffusive and substantive.

It has now be found that certain compounds can be developed that are stable to discolouration and yet are substantive, diffusive and possess the desirable spicy and anisic odour notes.

Accordingly, the invention provides in one of its aspects the use of compound of formula I as flavour or fragrance



I

wherein

i) the bond between C_1 and C_2 is a single bond;
R^1 is methyl, ethyl, *i*-propyl, *n*-propyl;
R^2 and R^3 are independently hydrogen or methyl; or
R^2 and R^3 taken together is a divalent radical $(CH_2)_n$, $C(CH_3)_2$, or $CH(CH_3)$ which forms a cycloalkane ring together with the carbon atoms to which it is attached;
R^4 and R^5 are independently hydrogen or methyl; or
R^4 and R^5 taken together is a divalent radical $(CH_2)_n$, $(CH_2)_{n-1}CH(CH_3)_2$, or $(CH_2)_{n-1}CH(CH_3)$ which forms a cycloalkane ring together with the carbon atoms to which it is attached;
n is an integer of 1, 2, 3, or 4; and
wherein at least one cycloalkane ring is present; or

ii) the bond between C_1 and C_2 together with the dotted line represents a double bond;
R^1 is methyl, ethyl, *i*-propyl, *n*-propyl;
R^2 is hydrogen or methyl;
R^3 and R^4 together is hydrogen or methyl; and
R^5 is hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *n*-butyl, *tert*-butyl or *sec*-butyl.

The compounds of formula I may comprise one or more a chiral centres and as such may exist as a mixture of stereoisomers, or they may be resolved as isomerically pure forms. Resolving stereoisomers adds to the complexity of manufacture and purification of these compounds, and so it is preferred to use the compounds as mixtures of their stereoisomers simply for economic reasons. However, if it is desired to prepare individual stereoisomers, this may be achieved according to methodology known in the art, e.g. preparative HPLC and GC or by stereoselective syntheses.

Particularly preferred compounds of formula I wherein the bond between C_1 and C_2 is a single bond are 1-cyclopropylmethyl-4-methylsulfanyl-benzene, 1-cyclobutylmethyl-4-methylsulfanyl-benzene, 1-cyclopentylmethyl-4-methylsulfanyl-benzene and 1-cyclohexylmethyl-4methylsulfanyl-benzene.

Particularly preferred compounds of formula I wherein the bond between C_1 and C_2 together with the dotted line is a double bond are 1-prop-1-enyl-4-methylsulfanyl-benzene and 1-hex-1-enyl-4-methylsulfanyl-benzene.

Compounds of formula I may be used alone or as a mixture to form a fragrance composition, which composition forms another aspect of the present invention. In addition, the compounds may be used in combination with other known flavourant or odourant molecules selected from the extensive range of natural and synthetic molecules currently available and/or in admixture with one or more ingredients or excipients conventionally used in conjugation with odourants or flavourants in fragrance or flavour compositions.

Compounds of formula I may be combined with a wide range of known odorants to create interesting odor notes. The following non-limiting list comprises examples of known odourant molecules which may be combined with the compounds of the present invention:

natural products: tree moss absolute, basil oil, tropical fruit oils (such as bergamot oil, mandarin oil, etc.), mastix absolute, myrtle oil, palmarosa oil, patchouli oil, petitgrain oil, wormwood oil, lavender oil, rose oil, jasmin oil, ylang-ylang oil.

alcohols: farnesol, geraniol, linalool, nerol, phenylethyl alcohol, rhodinol, cinnamic alcohol, (Z)-hex-3-en-1-ol, menthol, α-terpineol.

aldehydes: citral, α-hexyl cinnamaldehyde, Lilial, methylionone, verbenone, nootkatone, geranylacetone.

esters: allyl phenoxyacetate, benzyl salicylate, cinnamyl propionate, citronellyl acetate, decyl acetate, dimethylbenzylcarbinyl acetate, dimethylbenzylcarbinyl butyrate, ethyl acetoacetate, cis-3-hexenyl isobutyrate, cis-3-hexenyl salicylate, linalyl acetate, methyl dihydrojasmonate, styralyl propionate, vetineryl acetate, benzyl acetate, geranyl acetate.

lactones: γ-undecalactone, δ-decalactone, pentadecanolide, 12-oxahexadecanolide.

acetals: Viridine (phenylacetaldehyde dimethylacetal).

other components often used in perfumery: indole, p-mentha-8-thiol-3-one, methyleugenol, eugenol, anethol.

The compounds of the present invention may be used neat and simply admixed to form compositions. Alternatively or additionally however, they may be entrapped with entrapment materials, for example, polymers, capsules, microcapsules and nanocapsules, liposomes, film formers, absorbents such as carbon or zeolites, cyclic oligosaccharides and mixtures thereof, or they may be chemically bound to substrates which are adapted to release the compound of formula I upon application of an exogenous stimulus such as light, enzyme, or the like, and these entrapped forms may be used in compositions of the present invention.

The compositions may optionally comprise other excipients well known in the art, including anti-foaming agents, anti-oxidant agents, binders, colourants, diluents, disintegrants, emulsifiers, enzymes, fats, flavour-enhancers, flavouring agents, gums, lubricants, polysaccharides, preservatives, proteins, solubilisers, solvents, stabilisers, sugar-derivatives, surfactants, sweetening agents, vitamins, waxes, and the like. Solvents which may be used are known to those skilled in the art and include e.g. ethanol, ethylene glycol, propylene glycol, glycerol, triacetin, diethyl phthalate and dimethyl phthalate.

Examples of absorbents, entrapment materials, excipients, diluents or solvents for flavour or fragrance applications may be found e.g. in „Perfume and Flavor Materials of Natural Origin„, S. Arctander, Ed., Elizabeth, N.J., 1960; in "Perfume and Flavor Chemicals", S. Arctander, Ed., Vol. I & II, Allured Publishing Corporation, Carol Stream, USA, 1994; in "Flavourings", E. Ziegler and H. Ziegler (ed.), Wiley-VCH Weinheim, 1998, and "CTFA Cosmetic Ingredient Handbook", J.M. Nikitakis (ed.), 1st ed., The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, 1988.

The compounds of the present invention may be used in fragrance applications, e.g. in any field of fine and functional perfumery, such as perfumes, household products, laundry products, body care products and cosmetics. The high diffusion and substantivity of compounds according to the present invention are well perceived on fabrics washed with detergent or treated with a softener comprising them. The typical

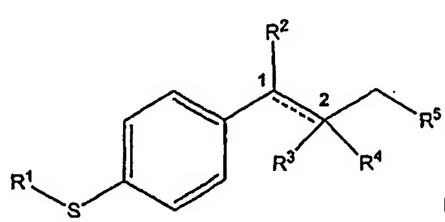
spicy anisic odour is already perceived on wet fabric and lingers for long periods, e.g. 2 – 4 days on dry fabric.

The compounds of formula I may be used in flavour applications and are useful in modifying for example, spicy flavours and seasonings for condiments and meats. They may be used in aromatic, herbal and spicy flavourings, heavy fruit flavours (e.g. raisin, prune) and in flavours for root beer. The compounds are also well suited for mouthwash applications.

In flavourant applications, the compounds of the formula I may be present in compositions in amounts ranging from 0.001 to 1000 mg/kg, more preferably from 0.05 to 500 mg/kg.

When used in fragrance applications, compounds of the formula I can be employed in widely ranging amounts depending upon the specific application, for example, from about 0.001 to about 10 weight percent. One application may be a fabric softener comprising about 0.001 to 0.05 weight percent. Another application may be an alcoholic solution comprising about 0.1 to 10 weight percent. The preferred concentrations vary between about 0.1 and 5 weight percent. However, the values are not limiting on the present invention, since the experienced perfumer may also achieve effects with even lower concentrations or may create novel accords with even higher amounts.

Whereas one compound has been described in the literature, others have not, and are novel. Thus, in an other aspect of the invention, there is provided a compound of formula I



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wherein R^1, R^2, R^3, R^4 and R^5 have the same meaning as given above with the proviso that if the bond between C_1 and C_2 together with the dotted line represents a double bond, R^1 is ethyl, R^2 is hydrogen, and R^3 and R^4 together is hydrogen, then R^5 is not hydrogen.

The compounds of formula I may be synthesised from commonly-available starting materials and reagents according to synthetic protocols known in the art. Benzene-(4-alkylsulfanyl-cycloalkyl) compounds of formula I (i.e. R^2 and R^3 forms a cycloalkane ring together with the carbon atoms to which they are attached) may be synthesised from the corresponding 4-alkylsulfanyl-phenyl carbonyl compound, e.g. 4-methylsulfanyl-benzaldehyde, under Wittig reaction conditions, followed by cycloalkylation of the intermediate alkylsulfanyl alkenyl benzene, e.g. 1-methylsulfanyl-4-propenyl-benzene, under Simmons-Smith reaction conditions, well known in the art.

Benzene-(4-alkylsulfanyl-cycloalkyl-methyl) compounds of formula I (i.e. R^4 and R^5 forms a cycloalkane ring together with the carbon atoms to which they are attached) may be synthesised from the corresponding 4-alkylsulfanyl-benzene, e.g. thioanisol ($C_6H_5SCH_3$), and the corresponding carboxylic acid chloride, e.g. cyclopropanecarboxylic acid chloride, followed by reduction of the intermediate ketone, e.g. cyclopropyl-(4-methylsulfanyl-phenyl)-methanone, under Wolff-Kishner reaction conditions well known in the art.

Further particulars as to reaction conditions are provided in the examples.

There now follows a non-limiting series of examples that illustrate the invention.

Example 1: 1-Prop-1-enyl-4-methylsulfanyl-benzene

To a cooled suspension (–10°C) of ethyl-triphenyl-phosphonium bromide (14.63g, 39.4 mmol) in THF was added BuLi (1.6 M solution in hexane, 24.6 ml). The mixture was stirred for 10 min and was then cooled to –78°C. 4-(Methylthio)-benzaldehyde (5.00g, 32.3 mmol) was added dropwise, the mixture was stirred for further 10 min and was then poured into a sat. solution of NH_4Cl. The mixture was diluted with pentane and the organic phase was separated, washed with water and brine and dried ($MgSO_4$). The residue was distilled bulb-to-bulb to yield 1-prop-1-enyl-4-methylsulfanyl-benzene (3.22g, 60%, mixture of E/Z isomers) as a colorless oil .

^{1}H-NMR ($CDCl_3$, 400MHz): 7.24-7.15 (m, 4H), 6.36-6.14/5.79-5.71 (2m, 2H), 2.46/2.44 (2s, 3H), 1.89-1.84 (m, 3H) ppm. MS (EI): 164 (M^+, 100), 149 (14), 117 (69), 115 (58), 91 (12), 77 (8), 63 (9), 51 (5). IR (atr): 3019w, 2919w, 1592w, 1492s, 1435m, 1092m, 964s, 836s, 780s cm^{-1}.

Odor description: anisic, minty, anethole

Example 2: 1-Hex-1-enyl-4-methylsulfanyl-benzene

Synthesized analogously to the procedure of Example 1.

^{1}H-NMR ($CDCl_3$, 400MHz): 7.24-7.14 (m, 4H), 6.35-6.12/5.66-5.59 (2m, 2H), 2.44/2.43 (2s, 3H), 2.35-2.16 (m, 2H), 1.47-1.29 (m, 4H), 0.91/0.89 (2t, J = 7.2 Hz, 3H) ppm. GC/MS (EI, major isomer): 206 (M^+, 80), 163 (100), 150 (21), 135 (14), 116 (92), 91 (9), 77 (5), 63 (4). IR (atr): 2956m, 2922m, 2857m, 1493s, 1436m, 1094m, 965s, 838m, 801m cm^{-1}.

Odor description: sassafras, fruity, pear, agrestic

Example 3: 1-Cyclobutylmethyl-4-methylsulfanyl-benzene

a) Cyclobutyl-(4-methylsulfanyl-phenyl)-methanone

Cyclobutane carboxylic acid chloride (4.50g, 38 mmol) dissolved in dichloroethane (10 ml) was added dropwise to a cold (–10°C) suspension of $AlCl_3$ (4.81g, 38 mmol) in dichloroethane (20 ml). To this solution was added methylsulfanyl-benzene (4.49g, 36 mmol) at such a rate that the temperature did not exceed 10°C. After the mixture was stirred for 45 min in an ice bath, it was poured on water and extracted with dichloroethane. The organic phase was separated, washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield a crystalline solid (6.78g, 91%).

^{1}H-NMR ($CDCl_3$, 400MHz): 7.81-7.79 (m, J = 6.8 Hz, 2H), 7.27-7.24 (m, J = 6.8 Hz, 2H), 3.95 (quint., J = 8.5 Hz, 1H), 2.51 (s, 3H), 2.47-2.23 (m, 4H), 2.13-2.03 (m, 1H), 1.95-1.86 (m, H) ppm. GC/MS (EI): 206 (M^+, 18), 178 (2), 151 (100), 123 (7), 108 (8), 79 (5), 45 (6).

b) 1-Cyclobutylmethyl-4-methylsulfanyl-benzene

A suspension of crude cyclobutyl-(4-methylsulfanyl-phenyl)-methanone (6.78g, 33 mmol), K_2CO_3 (1.82g, 13 mmol), and diethylene glycol was heated to 90°C and hydrazine hydrate (3.96g, 66 mmol) was added during 10 min. The mixture was further heated to 210°C for 20 min. After the mixture was cooled to room temperature, it was diluted with hexane and the organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled bulb to bulb to yield 2.72g (43%) of a colorless oil.

^{1}H-NMR ($CDCl_3$, 400MHz): 7.17-7.15 (m, J = 6.5 Hz, 2H), 7.05-7.03 (m, J = 6.5 Hz, 2H), 2.63 (d, J = 7.6 Hz, 2H), 2.56-2.46 (m, 1H), 2.42 (s, 3H), 2.05-1.97 (m, 2H), 1.87-1.78 (m, 2H), 1.73-1.64 (m, 2H) ppm. GC/MS (EI): 192 (M^+, 59), 164 (33), 137 (100), 122 (18), 117 (38), 115 (24), 91 (15), 78 (6), 55 (8). IR (atr): 2969m, 2921m, 2858w, 1493s, 1438m, 1097m, 832m, 802m cm^{-1}.

Odor description: floral, sassafras, cinnamic, sweet

Example 4: 1-Cyclopropylmethyl-4-methylsulfanyl-benzene

Synthesized analogously to the procedure of Example 3.

^{1}H-NMR ($CDCl_3$, 400MHz): 7.21-7.15 (m, 4H), 2.48 (d, J = 6.8 Hz, 2H), 2.44 (s, 3H), 0.99-0.89 (m, 1H), 0.56-0.44 (m, 2H), 0.23-0.12 (m, 2H) ppm.
GC/MS (EI): 178 (M^+, 57), 150 (28), 137 (100), 122 (21), 91 (21), 78 (10), 63 (6). IR (atr): 3075w, 3000w, 2919w, 1493m, 1016m, 814s, 651w cm^{-1}.

Odor description: fresh, sassafras, tarragon, agrestic

Example 5: 1-Cyclopentylmethyl-4-methylsulfanyl-benzene

Synthesized analogously to the procedure of Example 3.

^{1}H-NMR ($CDCl_3$, 400MHz): 7.19-7.17 (m, J = 6.5 Hz, 2H), 7.10-7.08 (m, J = 6.5 Hz, 2H), 2.56 (d, J = 7.6 Hz, 2H), 2.46 (s, 3H), 2.11-1.99 (m, 1H), 1.73-1.47 (m, 6H), 1.22-

1.13 (m, 2H) ppm. GC/MS (EI): 206 (M^+, 25), 137 (100), 122 (11), 91 (6), 78 (3), 41 (7). IR (atr): 2948s, 2919m, 2865m, 1493s, 1438m, 1097m, 967m, 829m, 794m cm^{-1}.

Odor description: floral, sassafras, cinnamic, sweet.

Example 6

A woody, spicy fragrance was made with the following ingredients

	parts per weight
Linalyl acetate	20.0
Ambrettolide™	6.0
Bois de Gaiac ess. Paraguay	8.0
Ethylene brassylate	200.0
Calone™ 10 % in DPG	3.0
Cardamome grains ess.	3.0
Cashmeran ™	1.0
Cassis base 345 FH	8.0
Citron ess.	35.0
Cyclohexal	50.0
Dihydro myrcenol	70.0
Dipropylene glycol	167.0
Fixobois 66606 B	25.0
Galaxolide™ 50 PHT	150.0
ISO E Super ™	95.0
Lavander ess. Barreme type	7.0
Linalool synth.	10.0
Mandarine Italie Orpure	5.0
Nirvanolide ™	13.0
Nutmeg ess. Indonesia	7.0
Pyralone 10% in DPG	2.0
Thibetolide™	75.0
Velvione™	40.0
1-Cyclopropylmethyl-4-methylsulfanyl-benzene	3.0
	1000

In this woody spicy fragrance, 1-cyclopropylmethyl-4-methylsulfanyl-benzene blends excellently with the fresh spicy and woody notes of the perfume. The compound imparts a full body spicy impression to the top note but also gives freshness to the spicy woody notes of the dry down.